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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

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TITLE OF THE INVENTION (280 characters max)

BIODEGRADABLE CERAMIC FIBRES FROM SILICA SOLS

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of

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for

BIODEGRADABLE CERAMIC FIBRES FROM SILICA SOLS

BIODEGRADABLE CERAMIC FIBRES FROM SILICA SOLS

TECHNICAL FIELD OF THE INVENTION

The present invention is directed to methods for preparing controllably biodegradable silica fibres. Specifically, the present invention is directed to methods for preparing controllably biodegradable silica fibres comprising spinning the fibres from a silica sol, the viscosity of the sol being controlled. Further, the invention is directed to controllably biodegradable silica fibres prepared according to the present invention. The present invention is further directed to methods for controlling the biodegradation of the silica fibres. The invention is also directed to controllably biodegradable silica fibres as sustained and/or controlled release delivery devices for biologically active agents, especially medicines, proteins, or hormones, and to pharmaceutical preparations comprising the devices.

BACKGROUND OF THE INVENTION

The sol-gel derived ceramic materials have many applications in various fields. Bioceramics is one of the most promising and interesting fields that still needs much development work for optimizing the properties of the ceramic material in the biological environment. The sol-gel process starting from a liquid phase enables an easy control of the pore structure of the material and an introduction of other components in different kinds of composites, especially, in

the case of silica-based materials. The processing of sol-gel derived silica fibres is known, and the main parameters controlling the process are the functionality of the silica precursors and the degree of branching of the silica clusters. The latter critically affects the spinnability and has commonly been characterized by rheological measurements.

Fibres have traditionally been used to improve mechanical properties of materials. In the case of the sol-gel derived silica fibres, there are two main parameters that determine the fibre bulk structure. Heat treatment of the fibres is one way to condense the bulk structure. Depending on the application of the sol-gel derived biodegradable silica fibres, the balance between mechanical properties and biodegradation may vary. For example, the mechanical properties are of minor importance when the silica fibre is used as a drug delivery device in a soft tissue. However, the mechanical properties have to be good enough to further process the obtained fibres to a desired form after the spinning. The biodegradation of the silica fibre decreases remarkably after the heat-treatment at high temperatures simultaneously as the mechanical properties become better.

International patent publication No. WO 97/45367 discusses sol-gel produced silica-xerogel materials. Patent publication DE 19609551 discusses silica fibres obtained by drawing them from a specific spinning composition. Neither of the patent publications teaches or suggests a controllably biodegradable silica fibre, a delivery device, or a pharmaceutical composition according to the invention or methods for preparing or using the same. Further,

neither of the patent publications teaches or suggests a method according to the invention for controlling the biodegradation of a silica fibre.

SUMMARY OF THE INVENTION

It has been found that the biodegradation of silica fibres can be controlled by controlling the viscosity of the spinning solution and, thus, the biodegradation of the silica fibres can be varied even when the same recipe is used. Accordingly, an object of the present invention is to provide a method for preparing controllably biodegradable silica fibres. Specifically, the present invention provides a method for preparing a controllably biodegradable silica fibre, wherein the method comprises spinning the fibre from a silica sol, wherein the viscosity of the silica sol is controlled. More specifically, the present invention provides a method for preparing a controllably biodegradable silica fibre, wherein the method comprises spinning the fibre from a silica sol, wherein the starting point of the spinning process is controlled by the viscosity of the silica sol.

It should be noted that the term spinning encompasses all of the suitable methods for preparing silica fibres from a silica sol.

A further object of the invention is to provide a controllably biodegradable silica fibre spun from a silica sol. Specifically, the present invention provides a controllably biodegradable silica fibre spun from a silica sol, wherein the biodegradation of the fibre is controlled by controlling the viscosity of the spinning sol. More specifically, the present invention provides a controllably biodegradable silica fibre spun from a silica sol having a viscosity of 1000-25000

mPas (milliPascalsecond). The fibre of the present invention is preferably heat-treated, to initially dry the fibre, only at low temperatures not harmful to biologically active agents, and it is not otherwise externally densified.

A further object of the invention is to provide sustained and/or controlled release delivery devices for biologically active agents, especially medicines, proteins, or hormones which are made of controllably biodegradable silica fibres, and pharmaceutical preparations comprising such devices.

A further object of the present invention is a method for controlling the biodegradation of silica fibres. The method comprises controlling the viscosity of the spinning sol or controlling the viscosity of the silica sol at the starting point of the spinning process.

Also, an object of the present invention is to provide a method for administering a biologically active agent to a human or animal which comprises implanting, injecting, or mucosally attaching to a human or animal a delivery device made of controllably biodegradable silica fibres of the present invention, in which structure a biologically active agent is incorporated.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a thermogravimetric spectra of the green state fibre samples aged for 3 months.

Figure 2 shows a derivative of the thermogravimetric spectra of Figure 1.

Figure 3 shows an FT-IR spectra of the fibre samples heat-treated in the

thermogravimetric analysis.

Figure 4 shows a transmission electron micrograph of the green body of FIB2_B aged for 3 months.

Figure 5 shows the biodegradation of the green state fibres aged for 3 months.

Figure 6 shows the release of dexmedetomidine from the silica fibres of Example 4.

DESCRIPTION OF THE INVENTION

Applicants have discovered that the biodegradation of silica fibres can be controlled by controlling the viscosity of the spinning solution. The biodegradation of the fibres can be varied even when using the same recipe. The biodegradation of the fibres can be adjusted for desired purposes by controlling the viscosity of the spinning solution for determining the starting point of the spinning.

Factors affecting the viscosity are the stage of spinnability, the temperature of the silica sol and the amount of solvent in the spinning sol. The silica sol is spinnable within a certain time period, rather than at a single point, and the viscosity of the silica sol increases during that time period. The increasing viscosity has an influence on the orientation of the silica clusters during the spinning and, thus, affects the formed bulk structure. The fibres spun in the early stage of the spinnability period degrade more slowly in the simulated body fluid than the fibres spun in the later stage of the spinnability. The stage of

spinnability may differ depending on the spinning method.

Another parameter that controls the spinnability and the viscosity is the temperature of the silica sol which can be varied. The fibres spun from the silica sols having a higher viscosity at a lower temperature (e.g., 0 °C) degrade faster than the corresponding fibres spun at higher temperatures (e.g., 20 °C).

The method for preparing a controllably biodegradable fibre of the present invention comprises spinning the fibre from a silica sol, wherein the starting point of the spinning process is controlled by the viscosity of the silica sol. The viscosity of the silica sol at the starting point of the spinning process can vary in the range of 1000 - 25 000 mPas. Another method according to the present invention comprises spinning the fibre from a spinning sol, wherein the viscosity of the silica sol is in the range of 1000 - 25 000 mPas.

The controllably biodegradable silica fiber of the present invention is spun from a silica sol, the biodegradation of the fibre being controlled by controlling the viscosity of the spinning sol or by controlling the starting point of the spinning process by the viscosity of the silica sol. Specifically, the fibres are spun from a silica sol having the viscosity of 1000-25 000 mPas, preferably 2000 -15000 mPas, the fibres having the solubility of 0.01- 20 m-%/h , preferably 0.02 - 8.5 m-%/h, in the simulated body fluid (Ohtsuki, C. et al., *J. Non-Cryst. Sol.* 143, 1992, 84-92), respectively.

The silica sol can be prepared for example as described in WO 97/45367. For example, a silica sol can be prepared by allowing a silica-alkoxide, such as tetraethylorthosilicate (TEOS) or an organically modified silicate (ORMOSIL), to

react with water and optionally an organic solvent, e.g. ethanol or polyethylene glycol, or a combination of solvents, at low temperature, such as -20 °C to 100 °C, preferably at room temperature, in the presence of an acidic or a basic catalyst by hydrolysis and subsequent condensation reactions. The condensation may also be partial. The sol can be incorporated with ions, such as Na, K, P, Ca, Mg, Al, and B. The catalyst should be such that it would not harm the biologically active agent.

The methods that can be used for preparing the silica fibres according to the invention are known to those skilled in the art. A suitable method is any method suitable for preparing fibres from silica sol, and the term spinning is used in this context to describe any such method. The spinning techniques include, e.g., dry spinning or a centifugal method. In the dry spinning method, the silica sol is forced through a spinneret and the evaporation of the solvent promotes the gelation. For example, the spinning solution is kept in a closed container and an inert gas, preferably nitrogen gas, is led to the container to push the spinning solution to a gear pump, wherein the spinning solution is metered to the spinneret. Preferably, the container is temperature adjustable. There are also special methods that are based on dry spinning. These methods include, e.g., a method wherein the fibre is led to a suitable aerosol which promotes the gelation of the fibre or a method wherein dry spinning and wet spinning are combined. In the centrifugal method, the spinning solution is in a rotating chamber which extrudes fibres through the holes in the chamber wall.

The controllably biodegradable silica fibres of the present invention can be

used for delivery devices or pharmaceutical preparations that are, for example, implanted or injected into, or mucosally attached to a human or animal. Administration into any tissue, soft tissues or bone, is possible. This allows local application so that targeting of the biologically active agent release site is possible. Therefore, the maximum effect from the agent is received.

In this connection, a delivery device includes a silica fibre or a combination of silica fibres with a biologically active agent incorporated into the silica fibre structure. A pharmaceutical preparation, such as a granulate or a capsule, in this context is a preparation that comprises the delivery device and possibly additional excipients useful in pharmaceutical preparations. A medical device of the invention is also useful for orthopedic and surgical purposes and need not contain a biologically active agent incorporated into its structure. A medical device may be, e.g., a woven or nonwoven mat made of silica fibres, a knitted fabric or a braided cord. The delivery devices and medical devices of the invention can be prepared by spinlaying.

The controllably biodegradable silica fibres of the invention may be either stable fibres or filaments. The silica fibres can be a part of a fibre blend or a part of some other material that is not in the fibre form.

Introduction of biologically active agents into the porous structure of the fibre provides alternatives for the design of biomedical applications. Biodegradable and non-toxic materials that are able to work directly and locally in a human or animal are beneficial, for example, as implants used as drug delivery devices or temporary implants in bone repairs. The sol-gel derived silica fibres

according to the invention fulfill these requirements. The biologically active agents incorporated into the silica fibre structure are released controllably and they can be used for delivery devices or pharmaceutical preparations that are, for example, implanted or injected into, or mucosally attached to a human or animal. The biologically active agent can be any organic or inorganic agent that is biologically active. The biologically active agent can be, e.g., a medicine, a protein, a hormone, a living cell, a dead cell, a bacteria, a virus or a part thereof. Biologically active agents include those especially useful for long-term therapy, such as hormonal treatment, e.g., contraception and hormone replacement therapy and for the treatment of osteoporosis, cancer, epilepsy, Parkinson's disease, pain, and cognitive dysfunction. The suitable biologically active agents may be, e.g., anti-inflammatory agents, anti-infectives (e.g., antibiotics and antiviral agents, such as glindamycin, miconazole), analgesics and analgesic combinations, antiasthmatic agents, anticonvulsants (e.g., oxycarbazepine), antidepressants, antidiabetic agents, antineoplastics, anticancer agents (e.g., toremifene, tamoxifene, taxol), antipsychotics, antispasmodics, anticholinergics, sympatomimetics, cardiovascular preparations, antiarrythmics, antihypertensives, diuretics, vasodilators, CNS (central nervous system) drugs such as antiparkinsonism drugs (e.g., selegiline), steroidal hormones (e.g., estradiol, progesterone, nestorone), sedatives (e.g., medetomidine, dexmedetomidine, levomedetomidine), tranquilizers, and cognitive dysfunction drugs (e.g., atipamezole). The medicine can be in the form of a salt, such as selegiline hydrochloride, (-)-4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

hydrochloride, 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole hydrochloride, dexmedetomidine hydrochloride and toremifene citrate. The medicine can also be in the form of a free acid, such as ibuprofen; a free base, such as caffeine or miconazole; or a neutral compound, such as Z-2-(4-(4-chloro-1,2-diphenyl-but-1-enyl)phenoxy) ethanol. A peptide can be, e.g., levodopa, and a protein can be, e.g., an enamel matrix derivative or a bone morphogenetic protein.

An effective amount of a biologically active agent can be added to the reaction mixture at any stage of the process. For example, it can be mixed with the starting materials. It can also be added to the reaction mixture at the sol-stage before the condensation reactions take place, during the condensation reactions, or even afterwards. The precise amount employed in a particular situation is dependent upon numerous factors, such as the method of administration, type of mammal, the condition for which the biologically active agent is administered, the particular biologically active agent used, the desired duration of use, etc.

The following examples are merely intended to illustrate the present invention, and are not to be construed as being limitations.

EXAMPLE 1

Preparation of silica sols for spinning

The silica sols were prepared from TEOS (tetraethyl orthosilicate 98%, ALDRICH), deionized water (conductivity ~0.05 µS), ethanol (Aa, 99.5%, ALKO)

and HNO_3 (65%, Merck) or NH_3 (28%, Fluka) as catalysts using the sol-gel method. The molar ratios used are shown in Table 1.

Table 1. Silica sol compositions in molar ratios

	Molar ratio (r)			
Name	H_2O/TEOS	EtOH/TEOS	HNO/TEOS	NH_3/TEOS
FIB1 (A&B)	2	1	0.036	0
FIB2 (A&B)	2	1	0.1	0
FIB3	2	1	0.1	0.01

The spinning solution was prepared as follows. Ethanol was mixed with TEOS and nitric acid with water. The acid/water solution was added to the TEOS/ethanol solution under vigorous stirring and then the solution was poured in an evaporating dish. The lid of the dish is a special cooler which condenses the evaporating ethanol and leads it to a volumetric flask. The evaporating dish was placed into a water bath (40°C) and the solution was kept there until a desired amount of ethanol had evaporated (20-22 h). Evaporation of ethanol was used to reduce the overall process time after which all the sols were still spinnable. Table 2 shows the theoretical silica concentrations of the spinning solutions assuming that the net reaction is $nSi(OR)_4 + 2nH_2O \rightarrow nSiO_2 + 4nROH$ and that the evaporating fraction consists mostly of ethanol due to the relatively low temperature and the low water content (r=1) that is mostly consumed in the hydrolysis.

Table 2. Silica contents of the spinning solutions

Sample name	*$m(SiO_2)/[m(SiO_2)+ m(EtOH)]$ / wt-%*
FIB1_A	45.4
FIB1_B	45.4
FIB2_A	42.7
FIB2_B	42.7
FIB3	41.7

The sols were cooled to either 20°C or 0°C depending on the sample. When the spinning solution reached a certain level of viscosity, the spinning was started. A rotational viscometer with a disc shaped spindle (Brookfield LVDV II+) was used to define the point where the spinning was started. Because of practical problems due to the great batch sizes of the spinning sols, the obtained viscosity values were not absolute, but they were comparable to each other. The initial viscosity was the same for all sample sols when the spinning process was started. However, each sol recipe was used to spin fibres in two stages. The starting viscosity was 1.5-2 times higher in the second stage than in the first stage. Air bubbles were removed from the spinning solution under partial vacuum. If this had not been done the sol-gel filaments would have broken due to a discontinuous flow of the spinning solution.

Dry spinning was used to prepare the sol-gel fibres. The spinning solution was kept in a container whose temperature is adjustable. Nitrogen gas was led into the closed container to push the spinning solution to a gear pump. Nitrogen is a good choice for this purpose because then the spinning solution is prevented from contact with the humid air. The gear pump (Zenith 958736) with a capacity

of 0.6 ml/revolution metered the spinning solution to the spinning head. The spinneret was made of a gold/platinum mixture. The diameter of the holes was 0.065 mm and the lenght/diameter ratio was 1. The number of the holes was 6. The distance between the spinneret and the wind-up roll was adjusted to meet the demands of each fibre.

EXAMPLE 2

Characterization of the fibre structures

A thermogravimetric analysis (TGA) was performed on the green state fibres to measure the weight changes with a Netzsch TG-209 equipment (NETZSCH GmbH, Selb, Bavaria, Germany) with nitrogen as the protective gas and air as the purge gas. The sample holder was a ceramic alumina crucible and the background measurement was done with an empty crucible before the measurements. The mass losses during the heat-treatment of the fibres were measured with a temperature program including several steps, both isothermal and dynamic: isothermal for 15 minutes at 21°C, dynamic 21-150°C with 2°C / minute, isothermal for 60 minutes at 150°C, dynamic 150-700°C with 5°C / minute and isothermal at 700°C for 30 minutes. TGA was performed for the fibres aged in a desiccator at room temperature for 3 months. The analysis was done up to 700°C because higher temperatures are practically useless concerning biodegradable applications of silica. The results of the samples are

shown in Figure 1, and the derivative of the spectra is shown in Figure 2.

The physical appearances of the fibres and the quality of the fibre filament in the spinning process, shown in Table 2, seem to have a connection with the TGA measurements. The mass losses of the fibres were quite considerable (15-25%), which stresses that a careful control of the heat-treatment is required in order to avoid cracking problems. The mass losses of the fibres spun in the early stage of spinnability were not as great as those spun in the later stage of spinnability. The greatest difference started at about 300°C, where the organic matter usually starts to evaporate. Because the recipes were exactly the same for FIB1_A and FIB1_B, as well as for FIB2_A and FIB2_B, respectively, it is likely that some organic matter was captured in the fibre structure of the fibres spun in the early stage of spinnability. Also, the shift observed in the derivatives of the fibres spun in the later stage of spinnability (FIB1_B, FIB2_B and FIB3) indicates some differences in the evaporation of the organic matter and in the fibre structure.

The physical appearance of the fibres contributes suggestions. The black colour of the fibres spun in the early stage of spinnability indicate that they contain carbon residuals. FIB3, where both HNO_3 and NH_3 were used as catalysts, had intermediate properties, both in the TG analysis and in the physical appearance. The mass loss was greater than in FIB1_A and FIB2_A, but smaller than in FIB1_B and FIB2_B. Also the colour of the FIB3 fibre was something between white and black, i.e., brown, and the filament quality in the spinning process had analogous properties.

The best and continuous fibres were easiest achieved with FIB1_B and FIB2_B. There were some difficulties with FIB3, FIB1_A and FIB2_A (processed at 0°C to achieve high enough viscosity in spinning). The filaments broke easily and continuous fibre processing was more difficult.

The infrared absorption spectra were recorded between 400 and 4000 cm^{-1} using a Bruker IFS 66 FTIR spectrometer. The measurements were carried out with the Diffuse Reflectance Infrared Fourier Transformation (DRIFT) system. Potassium bromide was used as a background material. The resolution of the FTIR equipment was 4 cm^{-1}. The FT-IR measurements made for the fibres heat-treated in the thermogravimetric analysis are shown in Figure 3. The measurements gave information of the typical OH groups on the silica surface, but also two unusual peaks were detected in the fibres spun in the early stage of spinnability (FIB1_A and FIB2_A). The broad peak at 3400-3770 cm^{-1} includes peaks related to isolated single SiOH groups, isolated geminal groups, H-bonded hydroxyls and physically adsorbed water which additionally has a peak approximately at 1630 cm^{-1} (broad). Additionally, the shift in the peaks indicated by a line drawn in the graph suggested that some organic residuals were also detected here. The shift was analogous with the extra peaks observed for FIB1_A and FIB2_A and the slight shift for FIB3 contributed the intermediate physical appearance. Peaks related to Si-O-Si vibrations were observed at 1200-1100 (broad) and 800 cm^{-1}. The peaks at 1870 and 2000 cm^{-1} were the Si-O-Si overtone bands of silica. The peak at 1300-1400 cm^{-1} was not typical for silica, but NO_3^- stretching vibration was typically located there. The catalyst used in the

sol preparation process was HNO_3, which may have residuals left in the structure. The fibre structure was commonly condensed and the temperature increased from 450 to 700°C quite fast and was kept there only for 30 minutes. This means that the decomposition of nitrate was not very effective. The two interesting peaks at 2330 and 3050 cm^{-1} were clearly seen only for FIB1_A and FIB2_A, but they could not be directly related to any component present in the system. The only possibility was that the fibres contained carbon residuals which formed double bonds with hydrogen (3050 cm^{-1}) and oxygen (2330 cm^{-1}) observed at these points.

A scanning-transmission electron microscopy (JEOL, JEM 1200 EX) was used to illustrate the bulk structure of the green state fibres. The fibres were embedded in an epoxy resin (EPON 812). Propylene oxide was used as a solvent and epoxy embedding media DMP-30 and DDSA or MNA as an accelerator and hardeners (FLUKA), respectively. The hardened samples were cut with an ultramicrotome to a thickness of 60-70 nm and the cross sections of the fibres were analysed. A transmission electron micrograph of the cross section of FIB2_B is shown in Figure 4. The image was chosen as an example to show the inner structure of the sol-gel derived silica fibres. The images of all the five samples reminded each other. FIB2_B was suggested to be a representative example of the fibres because the filament quality was good and the fibres were easy to prepare. The white bar at the bottom of the image corresponds to 20 nm. The structure was typical for the sol-gel derived materials. The structure was not completely condensed, but it contained a lot of small pores of about 2-5 nm in

diameter, which indicates that the structure was formed from smaller silica units.

EXAMPLE 3

Biodegradation of the fibres

The biodegradation of the samples was studied *in vitro* using a simulated body fluid (SBF). The simulated body fluid was prepared by dissolving the reagent chemicals of NaCl, $NaHCO_3$, KCl, $K_2HPO_4 \cdot 3H_2O$, $MgCl_2 \cdot 6H_2O$, $CaCl_2 \cdot 2H_2O$ and Na_2SO_4 into deionized water. The fluid was buffered at a physiological pH of 7.40 at 37°C with tris(hydroxymethyl)aminomethane and hydrochloric acid.

Three pieces of each specimen were used to study the reactions of the sol-gel derived silica fibres in the SBF. Each sample (10 mg) was immersed in 50 ml of the SBF contained in a polyethylene bottle covered with a tight lid. Three samples of the SBF enclosed in bottles without a specimen were used as controls to examine the solution stability. The samples were immersed in the SBF fluid for 2 weeks, the bottles being placed in a shaking water bath (SBD 50. (shake 2: 36 mm, speed = 160)) having a constant temperature of 37°C. Sample solutions were monitored for silicon and calcium concentrations as a function of immersion time. The calcium concentrations were determined with atomic absorption spectrophotometer (AAS, Perkin-Elmer 460). The silicon concentrations were analyzed by a molybdenum blue-method (Koch, O.G. & Koch-Dedic, G.A., Siliconmolybdänblau-Verfahren, *Handbuch der*

Spurenanalyse, Springer-Verlag,1974, p. 1105) based on a reduction reaction with 1-amino-2-naphtol-4-sulfonic acid using a UV-Vis spectrophotometer (Hitachi Model 100-60). All samples were tested three times each in order to avoid inaccuracy problems and possible degradation differences depending on the distribution in the cross-sectional diameter of the fibres (30-80 µm, medium value 50 µm). The biodegradation (*in vitro* in the simulated body fluid) of the green state fibres aged for about one month and three months is summarised in Table 3. In addition, the biodegradation (*in vitro* in the simulated body fluid) of the green state fibres aged for about three months is presented in Figure 5.

Table 3. Silica solubility of the fibres soaked in the SBF.

Fibre Name	Aging time /months	Silica solubility in the SBF/ w-%/h *
FIB1_A	1	0.02
FIB2_A	1	0.03
FIB1_B	1	(0.8)**
FIB2_B	1	(0.9)**
FIB3	1	1.7
FIB1_A	3	0.03
FIB2_A	3	0.2
FIB1_B	3	0.7
FIB2_B	3	0.8
FIB3	3	1.4

* Calculated from the linear portion of the curves before the saturation level between 5 to 53 h of immersion.
**Estimation, the point at ~50 h is missing due to technical problems.

The same kind of analogy observed in the TG analysis and FT-IR measurements was also observed here. The fibres spun in the early stage of spinnability (FIB1_A and FIB2_A) degraded very slowly when compared to fibres

spun in the later stage (FIB1_B, FIB2_B). FIB3 again had some kind of intermediate properties. According to the obtained results, some kind of a plateau value or a saturation level was achieved after a few days of immersion in the SBF. The solubility rates (before the plateau level) of FIB1_B, FIB2_B and FIB3 were clearly faster than those of FIB1_A and FIB2_A. This indicates that the area of silica available for the degradation is greater in the structure of the fibres spun in the later stage of spinnability. As observed in Table 2, there were some differences in the degradations when the samples aged for 1 or 3 months were compared to each other. A clear difference was observed in FIB2_A. The rate of the solubility was greater for the sample aged for 3 months, as was the silica saturation level (~2 % for the sample aged for 1 month and ~5% for the sample aged for 3 months). For the fibres spun in the later stage (FIB1_B, FIB2_B and FIB3) there were no significant differences after 1 month or 3 months of aging. The values were practically the same indicating that the structures were quite stable. However, they all were clearly more soluble in the SBF than the fibres spun in the early stage of spinnability.

EXAMPLE 4

Preparation of silica fibres containing dexmedetomidine hydrochloride

A sol for the fiber spinning was prepared from TEOS, deionized water, HNO_3 and ethanol in 1/2/0.036/1 ratio. Ethanol was mixed with TEOS and nitric acid with water. The acid/water solution was added to the TEOS/ethanol solution

under vigorous stirring and then the solution was poured into an evaporating dish. The evaporation process was performed as described before. Dexmedetomidine hydrochloride was added after the ethanol evaporation (0.5 w-%). The viscosity was 1640 cP when the spinning process was started. The fibres were stored for 18 days in a desiccator at room temperature until the dissolution tests were carried out.

In vitro dissolution test

The dissolution profiles of dexmedetomidine hydrochloride and silica from silica fibres were studied using planar shaker at a constant temperature. 0.9 w-% NaCl solution was used as a dissolution medium. Each sample (10 mg) was immersed in 50 ml of NaCl solution. The rotation speed was 50 rpm and the temperature 37°C. The sink condition was maintained during the dissolution period.

The absorbance values of the dissolution samples were measured on an UV-visible spectrophotometer (Hewlett Packard 845/A, USA) at the maximum absorbance of dexmedetomidine hydrochloride, 220 nm. Degradation of the silica fibres was determined by measuring the dissolved $Si(OH)_4$ spectrophotometrically as a molybdenum blue complex at 820 nm.

Results

The release of dexmedetomidine hydrochloride was proportional to the square root of time kinetics at a rate of 6.9 $\%/h^{1/2}$. The silica fibre matrix

dissolved linearly at a rate of 0.16 %/h.

Those skilled in the art will recognize that while specific embodiments have been illustrated and described, various modifications and changes may be made without departing from the spirit and scope of the invention.

The references discussed herein are specifically incorporated by reference in their entirity.

Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

CLAIMS

1. A method for preparing a controllably biodegradable silica fibre, comprising spinning the fibre from a silica sol, wherein the starting point of the spinning process is controlled by the viscosity of the silica sol.

2. The method according to claim 1, wherein the viscosity of the silica sol at the starting point of the spinning process is from about 1,000 mPas to about 25,000 mPas.

3. The method according to claim 2, wherein the viscosity of the silica sol at the starting point of the spinning process is from about 2,000 mPas to about 15,000 mPas.

4. A method for preparing a controllably biodegradable silica fibre, comprising spinning the fibre from a spinning sol having a viscosity of from about 1,000 mPas to about 25,000 mPas.

5. The method according to claim 4, wherein the viscosity of the spinning sol is from about 2,000 mPas to about 15,000 mPas.

6. A controllably biodegradable silica fibre spun from a silica sol, the biodegradation of the fibre being controlled by controlling the starting point of the

spinning process by the viscosity of the silica sol.

7. The controllably biodegradable fibre according to claim 6, wherein the viscosity of the silica sol at the starting point of the spinning process is from about 1,000 mPas to about 25,000 mPas.

8. The controllably biodegradable fibre according to claim 7, wherein the viscosity of the silica sol at the starting point of the spinning process is from about 2,000 mPas to about 15,000 mPas.

9. A controllably biodegradable silica fibre spun from a silica sol, the biodegradation of the fibre being controlled by controlling the viscosity of the spinning sol.

10. The controllably biodegradable fibre according to claim 9, wherein the viscosity of the spinning sol is from about 1,000 mPas to about 25,000 mPas.

11. The controllably biodegradable fibre according to claim 10, wherein the viscosity of the spinning sol is from about 2,000 mPas to about 15,000 mPas.

12. A method for controlling the biodegradation of a silica fibre spun from a silica sol, wherein the method comprises controlling the viscosity of the spinning sol.

13. The method according to claim 12, wherein the viscosity of the spinning sol is from about 1,000 mPas to about 25,000 mPas.

14. The method according to claim 13, wherein the viscosity of the spinning sol is from about 2,000 to about 15,000 mPas.

15. A method for controlling the biodegradation of a silica fibre spun from a silica sol, wherein the method comprises controlling the viscosity of the silica sol at the starting point of the spinning process.

16. The method according to claim 15, wherein the viscosity of the silica sol at the starting point of the spinning process is from about 1,000 mPas to about 25,000 mPas.

17. The method according to claim 16, wherein the viscosity of the silica sol at the starting point of the spinning process is from about 2,000 mPas to about 15, 000 mPas.

18. A delivery device comprising the controllably biodegradable fibre according to any one of claims 6 - 11, wherein the fibre contains a biologically active agent.

19. The delivery device according to claim 18, wherein the biologically active

agent is a medicine, a protein, a hormone, a living cell, a dead cell, a bacteria, a virus or a part thereof.

20. The delivery device according to claim 19, wherein the biologically active agent is a medicine.

21. A pharmaceutical preparation comprising a delivery device according to claim 18.

22. A method for administering a biologically active agent into a human or animal, wherein the method comprises implanting, injecting, or mucosally attaching a delivery device, wherein the delivery device comprises a controllably biodegradable silica fibre and wherein the silica fibre comprises a biologically active agent.

23. The method according to claim 22, wherein the biologically active agent is administered into a mammal.

ABSTRACT

The present invention relates to a method for preparing controllably biodegradable silica fibres. The method comprises spinning the fibres from a silica sol, the viscosity of the sol being controlled. Further, the present invention relates to controllably biodegradable silica fibres prepared according to the invention and methods for controlling the biodegradability of the fibres. The invention also relates to controllably biodegradable silica fibres as sustained and/or controlled release delivery devices for biologically active agents, and to pharmaceutical preparations comprising such devices.

FIGURE 1. A thermogravimetric spectra of the green state fibre samples aged for 3 months.

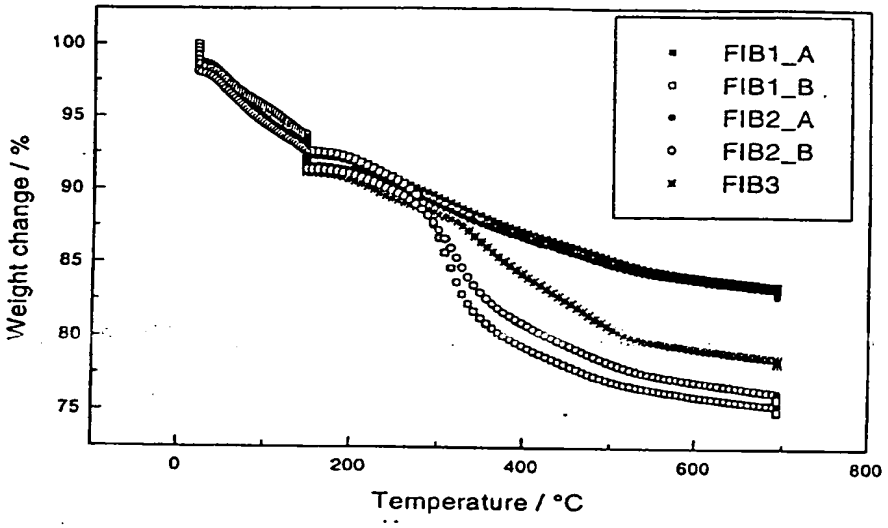

FIGURE 2. A derivative of the thermogravimetric spectra of Figure 1.

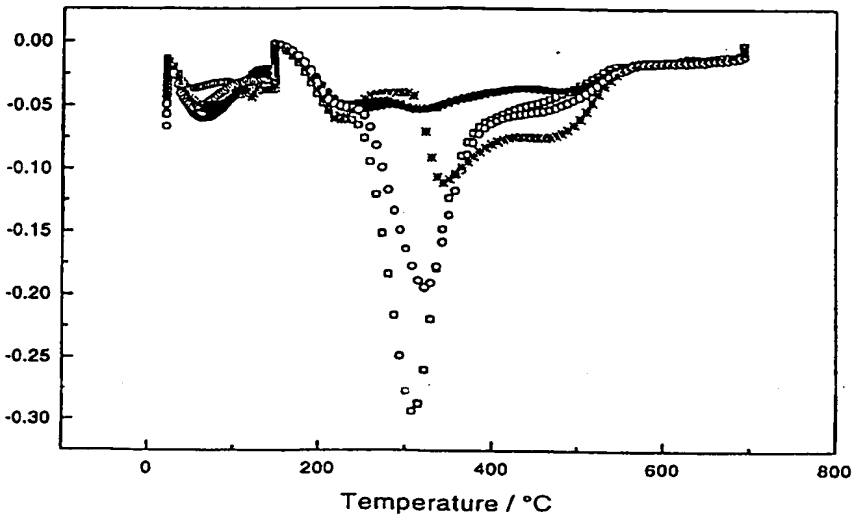

FIGURE 3. A FT-IT spetcra of the fibre samples heat-treated in the thermogravimetric analysis.

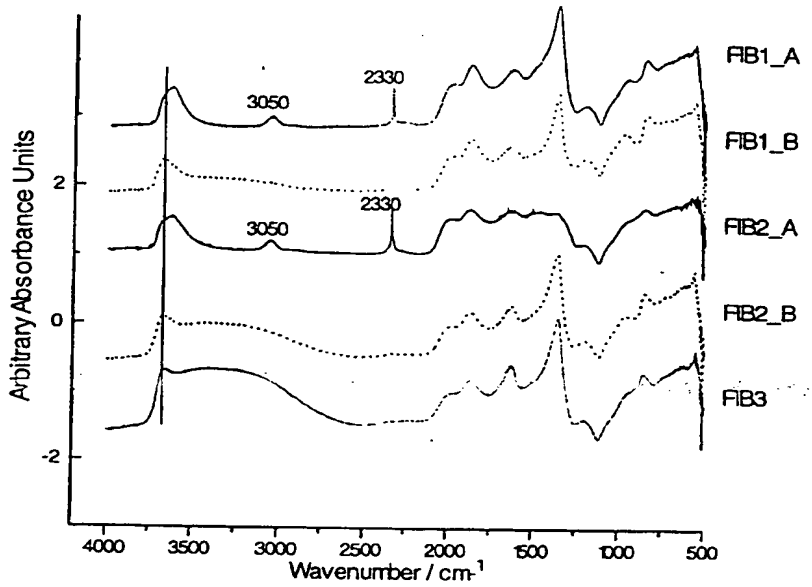

FIGURE 4. A transmission electron micrograph of the green body of FIB2_B aged for 3 months.

FIGURE 5. The biodegradation of the green state fibres aged for 3 months.

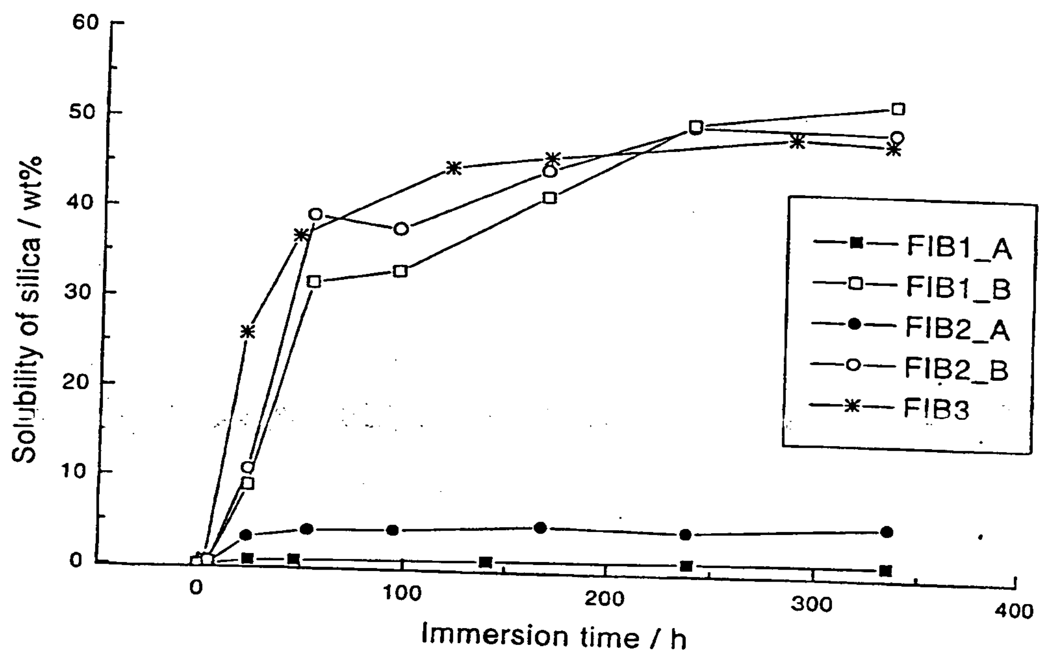

FIGURE 6. The release of dexmedetomidine from the silica fibres of Example 4.